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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/750,005	12/30/2003	Herbert T. Nagasawa	30451.2USU1	9934

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MANDEL & ADRIANO
SUITE 203
572 EAST GREEN STREET
PASADENA, CA 91101

EXAMINER	
HEARD, THOMAS SWEENEY	
ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/750,005	NAGASAWA ET AL.	
	Examiner	Art Unit	
	THOMAS S. HEARD	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *105-136* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *105-136* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/20/2007 has been entered.

Election/Restrictions

Newly submitted claims 126-136 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons as made on the Office Action mailed July 28, 2005:

Restriction to one of the following inventions is required under 35 U.S.C. 121

I. Claims 1-57, 94-104 are drawn to method of reducing oxidative stress classified in class 514, and subclass 2+.

II. Claims 58-93 are drawn to a pharmaceutical composition, classified in class 514, and subclass 2+.

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case CySSME can be used to

treat glutathione homeostasis and does not require the instantly method of administering CySSG, the Applicant's elected species.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;
(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;
(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);
(d) the prior art applicable to one invention would not likely be applicable to another invention;
(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 126-136 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Applicants have elected the species L-CySSG as the sulfhydryl protected glutathione prodrug in the reply to the original office action mailed 7/28/2005.

Claim(s) 105-136 are pending. Applicants have amended claim(s) by cancelling claims 1-104 previously pending and submitting the new claims of 105-136. Claims

126-136 are withdrawn by original presentation as set forth above. Claims 110, 117, and 124 are withdrawn as being drawn to non-elected subject matter. Claims 105-109, 111-116, 118-123, and 125 are hereby examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 106, 107, 113, 114, 120 and 121 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 106, 113, and 120 recites the limitation "glutathione produced via de novo glutathione biosynthesis pathway in the subject." There is insufficient antecedent basis for this limitation in the claim and it is indefinite as to how one can rely depend on a claim that clearly states that de novo synthesis is not a property yet state that de novo synthesis is part of the process.

In Claims 107, 114, and 121 the term derivative is not defined and is indefinite. Derivative could be nearly anything, including proteins that contain the glutathione or cysteine.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 105-109, 111-116, 118-123, and 125 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the relative skill of those in the art; (5) the predictability or unpredictability of the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method for providing glutathione to a subject without relying on de novo glutathione biosynthesis pathway comprising administering a sulfhydryl protected glutathione prodrug to a subject in need of such treatment, wherein the sulfhydryl protected glutathione prodrug produces glutathione in the subject without relying on the subject's own de novo glutathione biosynthesis pathway. Thus, the claims taken together with the specification implies the administration of L-CySSG, a naturally found component of the glutathione pathway for glutathione production, does not produce glutathione by the glutathione pathway.

(3) The state of the prior art:

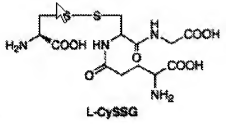
The state of the prior art as exemplified by Shirota et al, teaches the suppression of hepatotoxicity and oxidative stress induced by acetaminophen by the administration of the prodrug of L-cysteine, specifically that of CySSME. CySSME is a precursor to cysteine, which in turn is a precursor to GSH (Glutathione).

(4) The relative skill of those in the art:

The relative skill of those in the art is high.

(5) The predictability or unpredictability of the art: (6) The amount of direction or guidance presented and (7) The presence or absence of working examples: (8) The quantity of experimentation necessary:

Since the method of administering a glutathione precursor to a subject in need and have the composition that is composed of Cysteine and Glutathione (GSH) not use the Glutathione de novo pathway remains largely unsolved, and means for practicing the invention as such is highly unpredictable. Applicants elected species is as follows:



L-CySSG

The Compound is separated into two compounds of Cysteine and Glutathione (GSH), which are joined through the disulfide bond. Once administered, the disulfide would be reduced thereby cleaving the compound into Cysteine and Glutathione (GSH). The specification teaches at [0034] in the Patent Application Publication:

"In either case, the result would be the overall reduction of the disulfide bond leading to the net intracellular release of GSH as well as L-cysteine. Thus, a sulfhydryl protected glutathione prodrug such as CySSG provides not only GSH itself, but also L-cysteine **which is the key amino acid for de novo GSH biosynthesis**."

The specification has not provided any support for such a mechanistic property of CySSG. Further, the specification, in fact, states the opposite and appear to not know how the composition works. Considering the state of the art as discussed by Wands Factors supra and the high unpredictability and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention with the Applicant's elected species or any other compound and avoid the de novo Glutathione pathway. It is the examiner's position that one skilled in the art could not practice the invention commensurate in the scope of the claims without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 105-108, 111, 112-115, 119, 121, 122, and 125 are rejected under 35 U.S.C. 102(b) as being anticipated by Rathbun WB et al, "Prevention of acetaminophen- and naphthalene-induced cataract and glutathione loss by CySSME," Investigative Ophthalmology & Visual Science, Vol 37, 923-929. The instant invention is drawn to a method of providing glutathione to a subject (Claim 105), a method for maintaining glutathione homeostasis in a subject (Claim 112), and a method of maintaining cellular antioxidant levels in a subject in need of such treatment (Claims 119) through the single method step of administration of a sulfhydryl protected glutathione precursor.

Rathbun et al discloses the providing, maintenance of glutathione and cellular antioxidant levels through the administration of CySSME, a sulfhydryl protected glutathione prodrug. The administration of CySSME meets the limitation of Claims 107, 108, 111, 112, 114, 115, 118, 119, 121, 122, and 125 because it is administered and provided (Claims 105, 112, and 119), is a prodrug and a derivative (Claims 107, 114, and 121), and a pharmaceutical composition because of it administration to a mammal and cells, (Claims 108, 115, and 112). The reliance on the de novo glutathione biosynthesis pathway is not given patentable weight because the active step is administering, and once administered, must have any or all properties claimed in Claims

105, 112, and 119. Since the prior art teaches the active method step of administering same active agent (CySSME) to a subject, inherently glutathione would be provided to the subject without rely on de novo glutathione biosynthesis pathway. Therefore, the invention as claimed is anticipated by the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

For the purpose of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. V. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held in accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976);In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

Claims 105, 107-109, 111, 112-116, 118, 119-123, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over: Shirota FN, DeMaster EG, Shoeman DW,

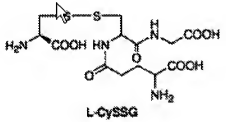
Nagasawa HT, "Acetaminophen-induced suppression of hepatic AdoMet synthetase activity is attenuated by prodrugs of L-cysteine," Toxicol Lett. 2002 Jun 7;132(1):1-8; Jonas AJ et al, "Cystine accumulation and loss in normal, heterozygous, and cystinotic fibroblasts," Proc Natl Acad Sci U S A. 1982 Jul;79(14):4442-5; and Bender AS et al, "Characterization of cystine uptake in cultured astrocytes," Neurochem Int. 2000 Aug-Sep;37(2-3):269-76.

Shirota et al teaches the suppression of hepatotoxicity and oxidative stress induced by acetaminophen by the administration of the prodrug of L-cysteine, specifically that of CySSME. Shirota et al teaches that the "hepatoprotection by cysteine generated from a prodrug, however, is due to enhanced GSH synthesis and maintenance of hepatic GSH homeostasis rather than to direct scavenging of the reactive-ACP metabolite by cysteine, see page 5, second column and last paragraph. Shirota et al does not teach the use of the naturally occurring, mixed-disulfide, L-Cysteine "prodrug" L-CySSG.

Jonas AJ teaches the administration of CSSG (the same as the Applicant's CySSG or L-CySSG) for the induction of Cystine in both normal, heterozygous, and cystinoic fibroblasts. Further, Bender A.S. et al teaches that "*the amino acid cystine is required for maintaining cellular levels of glutathione, a compound which protects cells against oxidative stress and various toxins (Meister and Anderson, 1983). Once taken up by cells, cystine is reduced to cysteine, the rate-limiting precursor of glutathione synthesis (Bannai and Teteishi, 1986).*"

The difference between what is instantly claimed and the prior art is that Bender AJ does not teach the administration of CySSG for CySSME and the production of GSH for the reduction of oxidative stress with a L-Cysteine producing compound.

It would have been obvious at the time of the instantly claimed invention to substitute CySSG for CySSME for the production of GSH and the reduction of oxidative stress due to the toxic dose of acetaminophen, or any other disease or malady that would benefit from maintaining cellular Glutathione levels, readable on Claims 105, 106, 108, 111, 112, 114, 115, 118, 119, 121, 112, 123, and 125. One would have been motivated to do so given Jonas' teaching that intracellular Cystine production can be induced with the administration of CySSG instantly claimed, and with Bender' teaching that Cystine is converted to cysteine, the precursor to GSH, one would be providing Glutathione, maintaining Glutathione homeostasis and cellular oxidative levels. Further, one would be further motivated to from the structure of CySSG, the Applicants elected species discussed and shown above,



L-CySSG

it is apparent that L-CySSG, once cleaved, produces **both** Glutathione (GSH) and Cysteine, and Cysteine is a precursor to GSH. Further too, given the CySSG is a naturally occurring product of the cell, the administration of L-CySSG would read on a dietary supplement. Finally, given that the steps are simply administrating CySSG, the

pathway is inconsequential regarding the de novo pathway because administering CySSG does not require knowledge of the pathway nor to perform the desired task. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention, because the administration of L-CySSG or CySSME both produce Glutathione and would maintain Glutathione homeostasis and cellular oxidative levels. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas S. Heard** whose telephone number is **(571) 272-2064**. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thomas S Heard/
Examiner, Art Unit 1654
Thomas S. Heard
United States Patent and Trade Office
Remsen 3B21
(571) 272-2064
Art Unit 1654

/Anish Gupta/
Primary Examiner, Art Unit 1654